IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	:	1615
Examiner	:	Micah Paul Young
Applicant(s)	:	Lorraine E. Pena *et al.*
Serial Number	:	10/072,493
Filed	:	February 5, 2002
For	:	COMPOSITION FOR RECTAL DELIVERY OF AN OXAZOLIDINONE ANTIBACTERIAL DRUG

Commissioner of Patents and Trademarks
Washington, DC 20231

DECLARATION BY DR. LORRAINE E. PENA, UNDER 37 CFR 1.132

Sir:

I, Dr. Lorraine E. Pena, declare that:

1. I am a joint inventor of the above-cited invention. I make this declaration in an attempt to further the prosecution of the application.

2. I received a B.S. degree in Chemistry and German from the University of Missouri - Kansas City, Kansas City, Missouri, in 1975, and a Ph.D. degree in Pharmaceutics from the same University in 1980.

3. I have many years of experience working in the development of formulations, including pharmaceutical formulations, with a particular emphasis on the development of antibiotic formulations, beginning at least as early as 1977. I have been a research scientist at what has recently become known as Pfizer Inc., at what was previously known as Pharmacia Corporation, known previously to that as Pharmacia & Upjohn, Inc, and known previously to that as The Upjohn Company (collectively referred to hereinafter as "Pfizer"), since at least as early as 1980. I was a Senior Research Scientist at what is now Pfizer since at least as early as 1988 until 2001, at which time my title changed to "Research Advisor." In my current capacity, I direct the research of formulators in the Liquids & Semisolids pharmaceutical formulations group at Pfizer's research facility in Kalamazoo, Michigan.

4. I am the author or co-author of at least eight publications and eighteen public presentations, many of which dealt with pharmaceutical formulations. I am also the inventor or co-inventor of at least three United States Patents, of at least seven published international patent applications, and of at least one published US application not yet published as an international application. A copy of my *curriculum vitae* is attached as Exhibit A.

5. I have reviewed an Office Action from the U.S. Patent and Trademark Office, mailed December 18, 2002, and portions of each of the references cited therein and herein-below, namely: Maillard *et al.* (U.S. Pat No. 3,712,675), Borgulya *et al.* (U.S. Pat. No. 5,574,055), Kaplan *et al.* (U.S. Pat No. 4,727,070), Barbachyn *et al.* (U.S. Pat. No. 5,574,055), "Linezolid" (*Drugs of the Future* 21(1): 116-1123, XP 000654643 (1996)), and Miyauchi (U.S. Pat. No. 4,900,730). The Office Action stated that all the claims of the subject patent application were "rejected under 35 U.S.C. 103(a) as being unpatentable over" Maillard *et al.*, Borgulya *et al.*, and Kaplan *et al.* "all in view of" Barbachyn *et al.*, "Linezolid", and Miyauchi. (Office Action, p. 4). I understand that the claims of the application will be amended in a response to the Office Action to be filed with the present Declaration.

6. I have reviewed a marked-up copy of the claims, showing the claims after amendment, attached hereto as Exhibit B. I understand that the amended claims are directed to a rectal composition and to a method of delivery of a composition comprising "at least one oxazolidinone in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone is poorly soluble, said composition being adapted for rectal administration..." (Language common to claims 1 and 21) I also understand that formula (I), used to define the "at least one oxazolidinone antibiotic drug" of amended claim 1, and formula (II), used to define the same term in claim 21 are identical.

7. For reasons provided below, I believe that the invention, as defined by the amended claims set forth in Exhibit B, would not have been obvious in view of what is stated in the Office Action about the references cited therein, and further in view of general knowledge known to one of skill in the field of the present claimed invention, at the time the present application was filed. I also submit that data in the specification of the above-cited patent application showed surprising results, not at all expected in view of what any of the six references cited

in the Office Action disclosed, or in view of general knowledge available to one of skill in the field of the present invention, at the time the present application was filed.

8. I understand that the first three references cited in the Office Action, Maillard, Borgulya *et al.*, and Kaplan *et al.* were each cited therein as teaching a "pharmaceutical composition comprising an oxazolidinone antibacterial agent dispersed in a lipophilic carrier." (Office Action, items 2, 3, and 4). I submit that none of the three cited references either disclose or suggest any oxazolidinone antibacterial drug, as that term is defined by formula (I) of claim 1 or by formula (II) of claim 21.

9. Kaplan *et al.* discloses a class of compounds that are "derivatives of the cephalosporin antibiotic, 7-[D-2-amino-2-(4-hydroxyphenyl)acetamido]-3-[(Z)-1-propenyl]ceph-3-em-4-carboxylic acid (BMY-28100)." (Kaplan *et al.*, col. 1, lines 6-12). Pharmaceutically acceptable metal and amine salts of the cephalosporin antibiotic are described as being "useful as dry pharmaceutical compositions because of their solid state stability." (Kaplan *et al.*, col. 4, lines 9-11). Kaplan *et al.* goes on to note that "strong aqueous acid ($pH \leq 1$) converts the metal and amine salts into the water insoluble form of the oxazolidinone products of the present invention." (*Id.*, lines 17-21). Nowhere does Kaplan *et al.* disclose or suggest that any such oxazolidinone derivatives of the metal and amine salts of the cephalosporin antibiotic are oxazolidinone antibiotic drugs, as defined by formula (I) of claim 1 or by formula (II) of claim 21 of the present application.

10. Example 7 of Kaplan *et* al. is also cited in the Office action as teaching "a dosage form comprising an oxazolidinone agent and a hard fat as a carrier." (Office Action, p. 3, item 4). However, Example 7 of that particular reference describes the manufacture of a suppository dosage form of sodium 7-[2,2-dimethyl-4-(4-hydroxyphenyl)-5-oxo-1-imidazolinyl]-3-[(Z)-1-propenyl]-ceph-3-em-4-carboxylate monohydrate, an imidazolidinone derivative of the cephlosporin antibiotic, not an oxazolidinone, much less the oxazolidinone antibiotic drug of formula I of the present invention. (Kaplan *et al.*, col 10, lines 1-3). The structure of the specific imidazolidinone derivative used in Example 7 of Kaplan *et al.* is shown in column 7, Example 1, of that reference. Upon information and belief, nothing in Kaplan *et al.* teaches or suggests the use of any oxazolidinone antibiotic drug of formula (I) of claim 1 or of

formula (II) of claim 21 in any pharmaceutical formulation or method of either claim, after amendment herein.

11. The compounds disclosed by Maillard and Borbulya *et al.* are oxazolidin-2-one derivatives. However, both sets of compounds differ from the "oxazolidinone antibiotic drug" of the formulations and methods of the present claims in structure, and none are described by either patent as being antibiotics. Specifically, Maillard describes the class of compounds disclosed therein as being useful as "analgesic and hypotensive drugs". (Abstract and col. 1, lines 40-42). Borbulya *et al.* teaches that the class of compounds disclosed in that patent are useful for the "control or prevention of depressive states, panic and anxiety states, cognitive disorders and neurogenerative diseases such as Parkinson's disease and Alzheimer's disease." (col. 1, lines 61-65).

12. In view of the above, I submit that nothing in the teachings of Maillard, Borbulya *et al.*, or Kaplan *et al.* discussed in the Office Action or herein above, that would have been likely to motivate one of skill in the art of the present invention to substitute any oxazolidinone antibiotic drug of formula (I) or of formula (II) of amended claims 1 or 21, respectively, of the present application, for the structurally and functionally dissimilar drugs in the rectal formulations of any of the three references.

13. I understand that Barbachyn *et al.* was cited in the Office Action as disclosing the specific formulation for "oxazolidinone antibiotic drug" now incorporated into claim 1. (Office Action, p. 5, second full paragraph). Barbachyn *et al.* was also cited in the Office Action as stating that a suppository formulation of compounds of the formulation could be made. (*Id.*, citing Barbachyn *et al.*, col. 6, lines 49-55). However, the reference fails to suggest that one could make a pharmaceutical composition suitable for rectal administration, "comprising at least one oxazolidinone antibiotic drug <u>in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone antibiotic drug is poorly soluble ...</u>" (Language common to claims 1 and 21, cited in paragraph 6, above, emphasis added.) Specifically, at no point does Barbachyn *et al.* teach or suggest the formation of a dispersion of solid particles of any oxazolidinone antibiotic drug in any medium in which the drug is poorly soluble.

14. I also understand that the "Linezolid" reference was cited in the Office Action as disclosing "a general formula of the [oxazolidinone antibiotic drug] of the invention." (Office Action, p. 5, third full paragraph). This reference does not even disclose a rectal formulation of any oxazolidinone antibiotic drug, much less suggest the pharmaceutical composition of the present invention, even when combined with all the references discussed above.

15. Finally, Miyauchi was cited by the Office Action as disclosing "a rectal suppository where the active antibacterial agents are micronized from 1-50 microns, and dissolved in the hard fat Witepsol H-15." (Office Action, p. 5, citing col. 5, lines 24-64, and Examples). A long list of drugs suitable for use in the formulations disclosed by Miyauchi are disclosed in column 5, lines 29-65, some of which are antibiotics; but, none of which are oxazolidinones. At no point does this reference suggest a pharmaceutical composition comprising a suspension of any antibiotic drug in a solid particulate form dispersed in a carrier in which the drug is poorly soluble, much less an oxazolidinone antibiotic drug of formula (I) or (II) of the present claims.

16. The six references discussed above each disclose various aspects of the present claimed invention. However, none of them, whether viewed individually or together appears to teach the elements common to both of claims 1 and 21 of the present invention, highlighted in paragraph 13 of the present Declaration, above. Furthermore, for reasons set forth below, upon information and belief, it would have been unexpected at the time the present invention was made for one to be able to produce a pharmaceutical composition of the present invention, a composition adapted for rectal administration.

17. The specification of the present application includes a description of an example of suppositories of an oxazolidinone antibiotic drug of formula (I) of amended claim 1, linezolid, produced by dissolution in a carrier (Example 2). Suppositories of linezolid dissolved in polyethylene glycol 4000 were prepared, with 20 mg of linezolid per suppository, close to the solubility limit of linezolid in the carrier medium. The data in Table 2 of Example 2, page 15, shows the concentration of linezolid in blood plasma found in four different dogs at various times after rectal administration of the 20 mg suppositories. This data was compared to suppositories of linezolid in solid particulate form, produced as described in the next paragraph, below.

18. In Example 5 of the present application, linezolid, in solid particulate form, was dispersed in a hard fat, Witepsol H-32, in which the drug is poorly soluble, and used to produce suppositories containing 600 mg of linezolid each. These suppositories were administered to each of four dogs in the same way as described in Example 2 (See preceding paragraph, above, for a brief summary of that study). The results of this second study are illustrated in Table 3, on page 17 of the present specification. Note that the amount of linezolid found in the blood plasma of each dog in this study is at least ten-fold higher at each time point assayed.

19. Upon information and belief, one of skill in the art of the present invention, at the time the present claimed invention was made, would not have expected a pharmaceutical composition comprising an oxazolidinone antibiotic drug of formula (I), as defined in amended claim 1 of the present application, to provide a composition suitable for rectal administration of the oxazolidinone antibiotic drug. Specifically, when such a drug is present in solid particulate form in a carrier in which it is poorly soluble, one would not expect the formulation to be suitable for rectal administration of the drug, for the following reasons. It was considered a general rule at the time the present invention was made that unless a drug is either present in dissolved form in the carrier of a rectal formulation or dissolves therein, it cannot be absorbed upon rectal administration. Nothing about the oxazolidinone antibacterial drug of formula (I) of amended claim 1 of the present application indicated that any such drug would be an exception to this general rule. In fact, linezolid was known to be poorly soluble in most lipophilic carriers, at the time the present invention was made.

20. Surprisingly, we found, that when pharmaceutical compositions of the present invention, comprising at least one oxazolidinone antibiotic drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone antibiotic drug is poorly soluble were rectally administered to a subject, the drug was absorbed into the subject. Specifically, we found that when one rectally administers to dogs suppositories of one such oxazolidinone antibiotic drug, linezolid, in which linezolid is present in solid particulate form in a carrier in which it is poorly soluble, in accordance with the methods of the present invention, a significantly higher amount of drug was released than one would

expect, given what was thought to be general knowledge in the art of the invention at the time the present invention was made, as described in paragraph 18, above.

21. This surprising and unexpected effect of use of the pharmaceutical compositions of the present invention has several consequences that were noted on page 3 of the present application. Specifically, it "allows for a smaller volume of the composition to be administered for a given dose; because, active agent loading is not limited by solubility in the carrier." (Specification, p. 3, lines 25-27). It also "makes the administration more practical and convenient to the subject," something particularly important where "the maximum tolerable volume of administration is small." (*Id.*, lines 27-30)

22. In summary, for reasons set forth above, in my review of the language of the six references cited in the Office Action as basis for the rejection described in paragraph 5, above, I submit that the Office Action and references as cited therein have not taught or suggested any pharmaceutical composition suitable for rectal administration, "comprising at least one oxazolidinone antibiotic drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone antibiotic drug is poorly soluble ..." (Language common to claims 1 and 21, cited in paragraph 11, above). Furthermore, for reasons set forth herein above, I submit that the specification of the present application illustrates that surprising and unexpected results were obtained upon rectal administration of at least one such compound.

23. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of an application or any patent issuing thereon.

Lorraine E. Pena

Lorraine E. Pena

Date: April 18, 2003

Curriculum Vitae
April 2003

Lorraine Elisabeth Pena, Ph.D.
Research Advisor
Pharmaceutical Sciences-Liquids & Semisolids-Unit 4836

Education: Ph.D., Pharmaceutics, University of Missouri-Kansas City, School of Pharmacy, Kansas City, Missouri, 1980
Major: Physical Pharmacy, Minor: Physical Chemistry
Thesis Title: Rheology and Solution Structure of Gum-Surfactant and Micelle Systems.

B.S., Chemistry & German, University of Missouri-Kansas City, Kansas City, Missouri, 1975.

Employment Experience:

2001-present	Research Advisor, Pharmaceutical Sciences-Liquids & Semisolids, Pharmacia Corporation, now Pfizer Inc., Kalamazoo, Michigan
1999-2001	Senior Research Scientist, Pharmaceutical Sciences-Liquids & Topicals, Pharmacia Corporation, Kalamazoo, Michigan
1998-1999	Senior Research Scientist, Pharmaceutical Development II-Pharmaceutical Product Development I, Pharmacia & Upjohn, Inc., Kalamazoo, Michigan
1996-1998	Senior Research Scientist, Pharmaceutical Development II-Consumer Products Development, Pharmacia & Upjohn, Inc., Kalamazoo, Michigan
1988-1996	Senior Research Scientist, Drug Delivery R&D-Specialty Products, The Upjohn Company, Kalamazoo, Michigan
1980-1988	Research Scientist, Pharmaceutical Manufacturing Technical Support, The Upjohn Company, Kalamazoo, Michigan
1978-1980	Graduate Teaching Assistant/Tutor, University of Missouri-Kansas City, School of Pharmacy, Kansas City, Missouri
1977-1978	Cosmetic Chemist, C.J. Patterson Company, Kansas City, Missouri

Honors: Upjohn Laboratories Special Recognition Award-Cyoctol Licensure 1990
TUC Bucks-Cortaid Cream Reformulation Project 1995
TUC Bucks-Preferred Materials PIT 1995
Pharmaceutical Development Special Recognition Award-Cleocin Ovule 2000
Global Supply Special Recognition Award-Cleocin Ovule 2000

Professional Affiliations: American Academy of Pharmaceutical Scientists
Society of Cosmetic Chemists

Products Developed: Kaopectate Bismuth Subsalicylate Formulations
Cleocin Vaginal Ovule
Cortaid Cream 1% Maximum Strength
Cleocin/Dalacin T Gel
Regaine Gel 2%
Progaine Shampoo
Topical Medrol 0.25% and 1.0%

US Patents and US and International Published Applications:

LE Pena, PB Bowman, RS Chao, CV Pesheck and CW Jacobsen, Composition and Method for Rectal Delivery of a Lincosamide Antibacterial Drug, US20020197320 A1, Published December 26, 2002.

LE Pena, PB Bowman, RS Chao, CV Pescheck, Intravaginal Clindamycin Ovule Composition, US 6,495,157, issued December 17, 2002; counterpart international application published as WO 01/10407 on February 15, 2001.

LE Pena, VE McCurdy and CS Clark, Composition for Rectal Delivery of an Oxazolidinone Antibacterial Drug, WO 02/072066 A1, Published September 19, 2002.

LE Pena and MS Wu, Novel Compositions of Minoxidil, WO 02/11698 A1, Published February 14, 2002.

LE Pena. Topical Pharmaceutical Compositions. WO 94/07478, Published April 14, 1994.

LE Pena and JL Peters. Self-Preserving Conditioning Shampoo Formulation. US 4,938,953, Issued July 3, 1990.

SM Peck, SC Valvani, LE Pena and CJ Thoennes. Foams for Delivery of Minoxidil. WO 88/01863, Published March 24, 1998.

DA Hatzenbuhler, JE Browne and LE Pena. Sebum-Dissolving Nonaqueous Minoxidil Formulation. WO 88/01502, March 10, 1998.

LE Pena. Minoxidil Gel. US 5,225,189, Issued July 6, 1993 & WO 89/07436, Published August 24, 1989.

Publications:

LE Pena, PL Possert, JF Stearns, BL Lee and MJ Hageman, "Rheological Characterization of rbSt Oil Suspensions", International Journal of Pharmaceutics, **113**, 89-96, 1995.

LE Pena, BL Lee and JF Stearns, "Structural Rheology of a Model Ointment", Pharmaceutical Research, **11**, 875-881, 1994.

LE Pena, BL Lee and JF Stearns, "Secondary Structural Rheology of a Model Cream", Journal of the Society of Cosmetic Chemists, **45**, 77-84, 1994.

LE Pena, BL Lee and JF Stearns, "Videomicroscopy Techniques for Agglomeration Studies", Pharmaceutical Research, **11**, 600-603, 1994.

LE Pena, BL Lee and JF Stearns, "Consistency Development and Destabilization of a Model Cream", Proceedings of the 16th IFSCC Congress, October 1990, New York. Also, Journal of the Society of Cosmetic Chemists, **44**, 337-345, 1993.

LE Pena, "Gel Dosage Forms-Theory, Formulation and Processing", in Topical Drug Delivery Formulations, DW Osborne and AH Amann, ed., Marcel Dekker, Inc., New York, New York, 1990.

LE Pena and BJ Sandmann, "Gel Development in Surfactant Systems", Second International Conference on Pharmaceutical Technology, Association de Pharmacie Galenique Industrielle, Paris, France, 1980.

LE Pena, "Rheology and Solution Structure of Gum-Surfactant and Micelle Systems", Doctoral Dissertation, University of Missouri-Kansas City, School of Pharmacy, Kansas City, Missouri, 1980.

Presentations:

Seminar Presentations:

LE Pena, BL Lee and JF Stearns, "The Impact of Shampoo Minor Components on the Degradation of Methylchloroisothiazolinone and Methylisothiazolinone", Annual Scientific Seminar, Society of Cosmetic Chemists, Las Vegas, Nevada, May 1994.

LE Pena, BL Lee and JF Stearns, "Consistency Development and Destabilization of a Model Cream", 16th IFSCC Congress, New York, October 1990.

LE Pena, "Gel Dosage Forms-Structure and Formulation", 61st Colloid and Surface Science Symposium, American Chemical Society, Ann Arbor, Michigan, June 1987.

LE Pena, "Rheology Case Studies of Topical Products", Midwest Regional Meeting, AAPS, Chicago, Illinois, May 1987.

LE Pena, "Sometimes It's the Little Things That Count", Symposium on Product Development Problems and Their Resolutions, AAPS National Meeting, Washington D.C., November 1986.

LE Pena and BJ Sandmann, "Liquid Crystalline Surfactant Systems.II. Rheology", Basic Pharmaceutics, Academy of Pharmaceutical Sciences Annual Meeting, San Antonio, Texas, November 1980.

BJ Sandmann, LE Pena and R Coveney, "Liquid Crystalline Surfactant Systems. I. Characterization", Basic Pharmaceutics, Academy of Pharmaceutical Sciences, Annual Meeting, San Antonio, Texas, November 1980.

LE Pena and BJ Sandmann, "Gel Development in Surfactant Systems", Second International Conference on Pharmaceutical Technology, Association de Pharmacie Galenique Industrielle, Paris, France 1980.

LE Pena and BJ Sandmann, "Rheological Characterization of Gum-Surfactant Systems", Basic Pharmaceutics, Academy of Pharmaceutical Sciences, Annual Meeting, Kansas City, Missouri, November 1979.

Poster Presentations:

LE Pena, GE Padbury, and BD Rush, "Rat Bioavailability Studies of the Chroman Amine Antioxidant U-83836E in Suspension and Solution", AAPS Annual Meeting, Indianapolis, Indiana, November 2000.

LE Pena, "*In Vitro* Drug Release Studies for Topical Products: An Overview of Parameters", Advances in the Biology and Treatment of the Skin, Environmental and Occupational Health Sciences Institute, Piscataway, New Jersey, June 1999.

LE Pena, "*In Vitro* Drug Release Studies for Topical Products: Experimental Studies", Advances in the Biology and Treatment of the Skin, Environmental and Occupational Health Sciences Institute, Piscataway, New Jersey, June 1999.

LE Pena and BL Lee, "*In Vitro* Drug Release Studies for Topical Products: An Overview of Parameters", AAPS 10th Annual Meeting, Miami Beach, Florida, November 1995.

LE Pena, BL Lee and JF Stearns, "*In Vitro* Drug Release Studies for Topical Products: Experimental Studies", AAPS 10th Annual Meeting, Miami Beach, Florida, November 1995.

BJ Sandmann, LE Pena and WA Strickland, Jr., "Ionization Properties of Minoxidil, Diisopropanolamine and Carbomer 934P in Mixed Solvent Systems", Midwest Regional Meeting AAPS, Chicago, Illinois, May 1993.

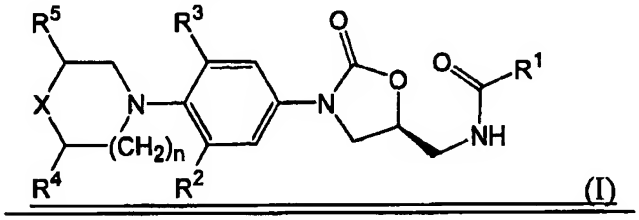
LE Pena, BL Lee and JF Stearns, "Videomicroscopy Techniques for Agglomeration Studies", Midwest Regional Meeting AAPS, Chicago, Illinois, May 1990.

DA Hatzenbuhler, JE Browne, DJ Whitaker, AE Zieve, KD Baker and LE Pena, "Rogaine Formulation Alternatives", Topical Drug Products Workshop, Arlington, Va., March 1990.

LE Pena, BL Lee and JF Stearns, "Secondary Structural Rheology of a Model Cream", Midwest Regional Meeting AAPS, Chicago, Illinois, May 1989.

PENA DECLARATION - EXHIBIT B

1. (currently amended) A pharmaceutical composition, comprising at least one oxazolidinone antibacterial drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone is poorly soluble, said composition being adapted for rectal administration, wherein the at least one oxazolidinone antibacterial drug is a compound of formula (I):



(I)

wherein:

R^1 is selected from (a) H, (b) C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy, C_{1-8} acyloxy or benzoxy groups, and including C_{3-6} cycloalkyl, (c) amino, (d) mono- and di(C_{1-8} alkyl)amino and (e) C_{1-8} alkoxy groups;

R^2 and R^3 are independently selected from H, F and Cl groups;

R^4 is H or CH_3;

R^5 is selected from H, CH_3, CN, CO_2R^1 and $(CH_2)_mR^6$ groups, where R^1 is as defined above, R^6 is selected from H, OH, OR^1, $OCOR^1$, $NHCOR^1$, amino, mono- and di(C_{1-8} alkyl)amino groups and m is 1 or 2;

n is 0, 1 or 2; and

X is O, S, SO, SO_2, SNR^7 or $S(O)NR^7$ where R^7 is selected from H, C_{1-4} alkyl (optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy, amino, C_{1-8} mono- or di(C_{1-8} alkyl)amino groups), and p-toluenesulfonyl groups;

or a pharmaceutically acceptable salt thereof.

2. (cancelled)

3. (original) The composition of Claim 1, wherein the solid particulate form of the at least one oxazolidinone has a volume median diameter of about 0.5 μm to about 150 μm.

4. (original) The composition of Claim 1 wherein the pharmaceutically acceptable carrier is lipophilic.
5. (original) The composition of Claim 4 wherein the lipophilic carrier is solid at room temperature.
6. (original) The composition of Claim 1 having a bioavailability of at least 25% of the total concentration of oxazolidinone in a dose of the composition administered to a subject.
7. (original) The composition of Claim 1, wherein the total concentration of oxazolidinone in the composition is sufficient to be effective for treatment and/or prophylaxis of a gram-positive bacterial infection in a subject when administered thereto.
8. (original) The composition of Claim 1 wherein the total concentration of oxazolidinone in the composition is about 0.1% to about 50% by weight.
9. (original) The composition of Claim 1 which is a dosage form selected from the group consisting of suppository, enema, microenema and rectal capsule.
10. (original) The composition of Claim 4 wherein the lipophilic carrier comprises a glyceride of fatty acids or a mixture of glycerides of fatty acids.
11. (original) The composition of Claim 10 wherein the lipophilic carrier comprises a hard fat.
12. (original) The composition of Claim 11 wherein the hard fat has a ß-polymorphic form which has a flow point of about 25°C to about 40°C.
13. (original) The composition of Claim 11 wherein the hard fat is a mixture of glyceride esters of vegetable C_{12}-C_{18} saturated fatty acids containing more than about 50% triglyceride esters.
14. (original) The composition of Claim 13 wherein the hard fat has an open-tube melting point of about 31-36°C in its α-polymorphic form; a solidification point of about 30-35°C in its α-polymorphic form; a hydroxyl value of not more than about 15 mg KOH/g; a saponification value of about 230-250 mg KOH/g; diglyceride content not more than about 15% by weight; and monoglyceride content not more than about 1% by weight.

15. (original) The composition of Claim 4 which is solid and has a weight of about 0.1 g to about 10 g.

16. (original) The composition of Claim 1, wherein the at least one oxazolidinone antibacterial drug has a particle size of less than about 20 μm.

17. (original) The composition of Claim 1 wherein the at least one oxazolidinone antibacterial drug is linezolid.

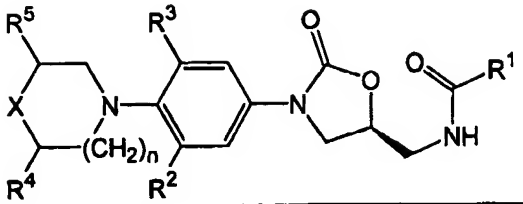
18. (original) The composition of Claim 1 wherein the at least one oxazolidinone antibacterial drug is N-[[(5*S*)-3-[4-(1,1-dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

19. (original) The composition of Claim 1, further comprising at least one antibacterial drug, other than an oxazolidinone, effective against gram-negative bacteria.

20. (original) The composition of Claim 19 wherein the at least one antibacterial drug effective against gram-negative bacteria is selected from the group consisting of: amikacin, ampicillin, azithromycin, aztreonam, carbapenam, cefazolin, ceftazidime, cefixime, ceftriaxone, cefoperazone, cefotaxime, ceftizoxime, cefuroxime, chloramphenicol, ciprofloxacin, clindamycin, colistin, domeclocycline, doxycycline, erythromycin, gentamicin, imipenem, levofloxacin, mafenide, methacycline, metronidazole, minocycline, neomycin, norfloxacin, ofloxacin, oxytetracycline, piperacillin, polymyxin B, pyrimethamine, silver sulfadiazine, sulbactam, sulfacetamide, sulfisoxazole, tetracycline, tobramycin, trimethoprim and quinolone.

21. (currently amended) A method of treatment or prevention of a gram-positive bacterial infection in a subject comprising:

(a) providing a pharmaceutical composition, comprising at least one oxazolidinone antibacterial drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone is poorly soluble, said composition being adapted for rectal administration, wherein the at least one oxazolidinone antibacterial drug is a compound of formula (II):



(II)

wherein:

R^1 is selected from (a) H, (b) C_{1-8} alkyl optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy, C_{1-8} acyloxy or benzoxy groups, and including C_{3-6} cycloalkyl, (c) amino, (d) mono- and di(C_{1-8} alkyl)amino and (e) C_{1-8} alkoxy groups;

R^2 and R^3 are independently selected from H, F and Cl groups;

R^4 is H or CH_3;

R^5 is selected from H, CH_3, CN, CO_2R^1 and $(CH_2)_mR^6$ groups, where R^1 is as defined above, R^6 is selected from H, OH, OR^1, $OCOR^1$, $NHCOR^1$, amino, mono- and di(C_{1-8} alkyl)amino groups and m is 1 or 2;

n is 0, 1 or 2; and

X is O, S, SO, SO_2, SNR^7 or $S(O)NR^7$ where R^7 is selected from H, C_{1-4} alkyl (optionally substituted with one or more F, Cl, OH, C_{1-8} alkoxy, amino, C_{1-8} mono- or di(C_{1-8} alkyl)amino groups), and p-toluenesulfonyl groups;

or a pharmaceutically acceptable salt thereof; and

(b) rectally administering the pharmaceutical composition to the subject.

22. (original) The method of Claim 21, wherein the solid particulate form of the at least one oxazolidinone provided in step (a) has a volume median diameter of about 0.5 μm to about 150 μm.

23. (cancelled)

24. (original) The method of Claim 21, wherein the total concentration of oxazolidinone in the pharmaceutical composition provided in step (a) is sufficient to be effective for treatment and/or prophylaxis of a gram-positive bacterial infection in the subject when administered thereto in step (b).

25. (original) The method of claim 21, wherein the pharmaceutical composition further comprises at least one antibacterial drug effective against gram-negative bacteria.

26. (original) The method of Claim 25 wherein the at least one antibacterial drug effective against gram-negative bacteria is selected from the group consisting of amikacin, ampicillin, azithromycin, aztreonam, carbapenam, cefazolin, ceftazidime, cefixime, ceftriaxone, cefoperazone, cefotaxime, ceftizoxime, cefuroxime, chloramphenicol, ciprofloxacin, clindamycin, colistin, domeclocycline, doxycycline, erythromycin, gentamicin, imipenem, levofloxacin, mafenide, methacycline, metronidazole, minocycline, neomycin, norfloxacin, ofloxacin, oxytetracycline, piperacillin, polymyxin B, pyrimethamine, silver sulfadiazine, sulbactam, sulfacetamide, sulfisoxazole, tetracycline, tobramycin, trimethoprim and quinolone.
27. (original) The method of claim 21 wherein the at least one oxazolidinone antibacterial drug is linezolid.
28. (original) The method of claim 27, wherein the subject is an adult human and about 400 to about 600 mg of the linezolid is administered rectally twice daily to the subject for a period of about 10 to about 28 days.
29. (original) The method of Claim 27, wherein the subject is a human child and about 8 to about 12 mg linezolid per kg body weight is administered rectally 2 to 3 times daily for a period of about 10 to about 28 days.